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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/623,728	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 February 2008 and 26 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

DETAILED ACTION

1. Applicant's response and amendments received February 8, 2008 and August 26, 2008 are acknowledged.

Claims 8-28 have been canceled.
Claims 1 and 4 have been amended.
Claims 1-7 are pending in this application.

Claims 1-7 are under examination as they read on fusion proteins comprising autoantigenic polypeptides associated with the disease Multiple Sclerosis.

Specification

2. Applicant's amendment to the specification received August 26, 2008 is objected to for the following informalities. Applicant has changes the formatting of biological sequences disclosed on page 28 of the specification as originally filed. As originally filed, the PLP-LR peptide identified as SEQ ID NO:2 had two amino acid residues underlined to graphically indicate where this sequence was modified from the naturally occurring sequence of PLP1 (aka SEQ ID NO:1). The revised paragraph does not retain the underlined sequence residues, although the text of the paragraph still indicates that amino acid residues are underlined. Appropriate correction is needed.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by WO 90/09804 (of record) has been withdrawn in view of applicant's claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NOs:1 and 2. These sequences are not disclosed by the '804 patent and thus the rejection has been withdrawn.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The rejection of claims 1, 3, 4, and 5 under 35 U.S.C. 103(a) as being unpatentable over Zanetti et al. (WO 90/09840, of record) in view of Liu et al. (International Immunology, 1995, 7:1255-1263) has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not disclosed by Zanetti et al. or by Liu et al. and thus the rejection has been withdrawn.

7. The rejection of claims 1, 3, 4, and 6 under 35 U.S.C. 103(a) as being unpatentable over Zanetti et al. (WO 90/09840, of record) in view of Karpus et al. (Journal of Neuroscience Research, 1996, 45:410-423) has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not disclosed by Zanetti et al. or by Karpus et al. and thus the rejection has been withdrawn.

8. The rejection of claim under 35 U.S.C. 103(a) as being unpatentable over Zanetti et al. (WO 90/09840, of record) in view of Liu et al. (International Immunology, 1995, 7:1255-1263) in view of Karpus et al. (Journal of Neuroscience Research, 1996, 45:410-423) as applied to claims 1-6 and 21-27 above, and further in view of Elliott et al. (J. Clin. Invest., 1996, 98:1602-1612) has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not disclosed by any of the cited references and thus the rejection has been withdrawn.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The rejection of claims 1-7 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of applicant's claim amendments received 2/8/08.

Specifically, the claims have been amended to recite a specific disease (multiple sclerosis) and two specific autoantigenic polypeptides associated said disease (SEQ ID NOs:1 and 2). These amendments address the issues raised in the rejection of record and thus the rejection has been withdrawn.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. The provisional rejection of claims 1-7 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 11/612,773 in view of Elliott et al. (J. Clin. Invest., 1996, 98:1602-1612) has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not recited in the claims of the '773 application and are not disclosed by Elliott et al. Thus the rejection has been withdrawn.

13. The provisional rejection of claims 1-4 and 6 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/619,568 has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not recited in the claims of the '568 application and thus the rejection has been withdrawn.

14. The provisional rejection of claims 1-4 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-60 of copending Application No. 10/510,411 has been withdrawn in view of the claim amendments received 2/8/08.

Specifically, the independent claim has been amended to recite the polypeptide sequences of SEQ ID NO:1 and SEQ ID NO:2. These sequences are not recited in the claims of the '568 application and thus the rejection has been withdrawn.

Claim Objections

15. The objection to claim 4 for the misspelling of the disease lupus has been obviated by the deletion of this limitation from the claimed invention.

16. Applicant's claim amendments received February 8, 2008 have successfully overcome all prior grounds of rejection. However, the claim amendments that successfully overcame said rejections have raised new issues and have necessitated the following new grounds of rejection.

17. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has amended the claims to recite a fusion product comprising SEQ ID NOs:1 and/or 2 that alleviates symptoms associated with multiple sclerosis (MS). On page 27 of the specification, PLP1 is defined as a peptide fragment of proteolipid protein (PLP) comprising amino acid residues 139-151, while PLP-LR is a peptide analog of PLP1 which does not activate PLP1 pulsed cells. Example 1 on page 28 discloses that PLP1 is SEQ ID NO:1, which is HSLGKWLGHPNKF. This example further discloses that PLP-LR is SEQ ID NO:2 which is HSLGK*L*LG*R*PNKF (mutations from PLP1 in italics). These two peptides were then used to construct immunoglobulin molecules comprising proteolipid peptides in place of the heavy chain CDRs, with the resulting molecules being designated as Ig-PLP1 and Ig-PLP-LR. Ig-PLP1 and Ig-PLP-LR were administered to mice in examples X-XXV. Some of these examples appear to

indicate that Ig-PLP1 and Ig-PLP-LR may inhibit the development of EAE, a mouse model that mimics some of the signs and symptoms of MS, if the molecules are administered at birth (example XIX), and that aggregated forms of the molecules may have therapeutic efficacy at later timepoints (example XXV).

However, peer-reviewed publications also discuss the administration of Ig-PLP1 and Ig-PLP-LR, such as Legge et al. (1997 and 1998, see entire documents). These non-patent disclosures indicate that the sequences of the PLP1 and PLP-LR peptides as being HSLGKWLGHPDKF and HSLGK*L*LG*R*PDKF respectively (differences from SEQ ID NOs:1 and 2 underlined). Amino acids 139-151 of mouse PLP are HSLGKWLGHPDKF (Kuchroo et al., see particularly the abstract). Human PLP is HCLGKWLGHPDKF (see enclosed sequence alignment). As such, human and murine wild type sequences comprise a D, rather than an N residue at the position corresponding to aa 149. Inspection of the figures disclosed by Legge et al. in their 1998 paper reveals them to bear striking similarities to those of the instant specification (for example, compare Figures 11 and 12 of the instant specification with Figures 2 and 3 of Legge et al.). Given that the peer-review data and the data of the instant specification appear to be similar and use fusion proteins identified by identical names, it is unclear if the fusion proteins disclosed in the instant specification are or are not the same as those disclosed in the peer reviewed literature. This issue is important because it appears that SEQ ID NO:1 and SEQ ID NO:2 are not naturally occurring sequences, and it appears that these sequences are not disclosed anywhere else excepting the instant specification and other patent applications that ultimately claim priority to the application which has issued as patent 6,737,057.

Thus, while no mechanism of action is recited for how the claimed fusion proteins alleviate MS symptoms, based upon the specification it appears that the peptides recited as being part of the claimed fusion proteins are required to induce tolerance to an altered self-peptide (since SEQ ID NOs:1 and 2 are not naturally occurring as discussed above) to treat the autoimmune disease MS. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results

have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively) but were unsuccessful in human applications.

As set forth above, the references demonstrate that even unsubstituted peptides (peptides that are not APLs, which SEQ ID NOs:1 and 2 are since they are non-naturally occurring sequences) that work in *in vivo* small animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001), teaches that:

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn"* (emphasis added).

A review of the instant specification reveals that a T cell response to PLP-1 can be inhibited in the experimental mouse model of EAE. As set forth above, experimental results in an EAE have failed to translate into effective treatments for autoimmune diseases, and the claimed fusion protein is recited as alleviating symptoms associated with multiple sclerosis.

Further, Applicant's subsequent work indicates that the claimed products do not necessarily comprise the recited functional attributes. See for example Legge et al. (1998). Therein the authors teach that APLs function as “T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient and thus cause exacerbation, rather than amelioration of disease symptoms. Thus, the recited products are reasonably expected not to comprise the recited biological activity.

A set forth in *Rasmusson v. SmithKline Beecham Corp.,* 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art “would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> “As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to “inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the “inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Even more recent work supports the rejection for lack of enablement. A review by Steinman (2007) teaches that, while antigen-specific immunosuppression would be desirable, it has generally failed in humans. In trials with even the most well studied MS-related antigen, myelin basic protein 83-98 (MBP83-98) in some instances administration of the antigen exacerbated disease and in other instances caused such severe hypersensitivity reactions that the trials had to be terminated prematurely (page 663). The Inventor's own work, Bell et al. (2008) further demonstrates that the claimed product may not comprise the recited biological activity. The reference teaches that administration of Ig-PLP1 exacerbated EAE in certain F1 mice (generated to more

closely model the outbred human population). As the Inventor concluded, "complex polymorphisms which could result in unbalanced MHC expression need to be taken into consideration to devise effective Ag-specific therapy against the disease". The instant application has a priority date of 1997, yet even presently it is not clear that the products claimed by applicant would actually serve to alleviate MS symptoms since many promising reagents identified in the EAE model have not been successfully applied to the human disease MS and because products that appear to be structurally related to those claimed by applicant appear to have exacerbated, rather than ameliorated, EAE in some mice. Note that all currently pending claims ultimately depend from claim 1 and thus all claimed products must comprise the ability to alleviate symptoms of MS.

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working examples specific for human disease the unpredictability of the art, and the breadth of the claims, it would take undue experimentation to make and use the instant claimed products.

18. Claim 1 is objected to for its potentially ambiguous language. Particularly, the phrase “one or more autoantigenic polypeptides or fragments thereof" is recited twice in the claim, yet upon close reading the claim appears to be limited to a fusion protein comprising SEQ ID NO:1 or SEQ ID NO:2 fused to an immunoglobulin fragment that binds an Fc receptor. Thus, in the interest of clarity and readability, it is suggested that the aforementioned phrase be deleted and the claim amended to recite just the Markush grouping. One possible example of how the body of the claim might be amended is as follows “…comprising an immunoglobulin or portion thereof linked to a polypeptide selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, wherein said immunoglobulin ….”.

19. No claims are allowable.

20. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka/
Primary Examiner, Art Unit 1644